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10/620,777	07/15/2003	Roy Curtiss III	56029/	1127

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EXAMINER	
GANGLE, BRIAN J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

The amendment filed on 5/5/2008 under 37 CFR 1.116, in reply to the final rejection, has been considered but is not deemed to place the application in condition for allowance. Said amendment is hereby entered.

Claims 61, 84, 89-90, and 94 are amended. Claims 61-75, 77-86, 89-90, and 94-103 are pending. Claims 65-66, 68-69, 74-75, 77-82, and 95-103 are withdrawn as being drawn to non-elected inventions. Claims 61-64, 67, 70-73, 83-86, 89-90, and 94 are currently under examination.

Claim Objections Withdrawn

The objection to claims 61-64, 67, 70-72, 83-86, 88-90, and 92-94, because the claims are drawn, in part, to non-elected subject matter, is withdrawn in light of applicant's amendment thereto.

The rejection of claims 88 and 91-94, as being duplicate claims, is withdrawn in light of applicant's amendment thereto.

New Claim Objections

Claim 73 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 73 includes the limitation that the essential gene is carried on an extrachromosomal vector, which is already a limitation of the parent claim.

Claim Rejections Withdrawn

The rejection of claims 61-64, 67, 70-73, and 83-94 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "viable," is withdrawn in light of applicant's arguments.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 61-63, 67, 70-73, and 83-84 under 35 U.S.C. 103(a), as being unpatentable over Galan *et al.* (Gene, 94:29-35, 1990) in view of Guzman *et al.* (J. Bacteriol., 177:4121-4130, 1995), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That there is no teaching or suggestion in either Galan or Guzman to create an environmentally limited viability system wherein a cell is viable in one environment and not viable in another. Applicant reiterates the teachings of Galan and Guzman, stating that Galan merely teaches the use of "balanced-lethal" technology, where the *asd* gene is deleted from the bacterial chromosome and is supplied on a plasmid, to serve as a selection pressure to maintain the plasmid. Applicant also states that there is no teaching or suggestion in Galan to regulate the expression of *asd* and state that *asd* is constitutively expressed in all environments.

2. That the examiner's "generalization" that one of skill in the art would have been motivated to link *asd* to the promoter of Guzman to study depletion phenotypes is hindsight reasoning. Applicant argues that because Galan teaches the function of *asd* and it's complementation, one would not have been motivated to use the teachings of Guzman to assess the effects of the expression or depletion of the gene product in mutants lacking the chromosomal gene.

3. That the examiner is conducting improper hindsight reconstruction to pick individual components of the invention and to make "bald conclusory statements regarding motivation, e.g., further general scientific study, without finding that motivation in the references themselves." Applicant further asserts that their combination of components, some of which were known at

the time of filing, creates a new and useful environmentally limited viability system to further promote the field of vaccines, and is neither taught nor suggested in any of the cited references.

4. That in their system, viability of the microorganisms is limited to the permissive environment by specifically expressing one or more genes essential to cell viability only while in the permissive environment. Applicant asserts that none of the cited references includes the concept of permissive and non-permissive environments paired to a particular chromosomal deletion and regulated expression of a non-chromosomal essential genetic element.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, despite applicant's assertions, Guzman clearly discloses an environmentally limited viability system wherein a cell is viable in one environment and not viable in another. Guzman shows that by linking the pBad promoter to an essential gene (*ftsQ*) that is missing from the chromosome, the cells require arabinose to survive. The only difference between the system of Guzman and the instant invention is that *ftsQ* is used rather than *asd*. Finally, applicant has stressed the fact that, in Galan, the *asd* gene is constitutively expressed, as if this somehow makes these cells unsuitable for the instant invention. It is noted that the "balanced-lethal" plasmid maintenance system is a preferred embodiment of the instant invention (see page 16, lines 25-30 of the instant specification).

Regarding argument 2, any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper. *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). In the instant case, the examiner has referenced motivations that were expressly stated in the art; thus, no improper hindsight reasoning was used. Applicant may disagree with the motivation presented, but this does not mean that hindsight reasoning was used.

While Galan does teach that *asd* is essential and that it's presence allows stable maintenance of plasmids, the promoter system of Guzman allows one to study the effects of a range of expression levels, not just presence and absence. Furthermore, they state that their promoter is a "simple and useful expression system for efficient repression, modulation, and moderately high expression" and that other promoters have the disadvantage of overexpression,

which can be detrimental for cell growth (page 4129 column 2). These are advantages and disadvantages that are expressly disclosed in the prior art and are not the product of hindsight reasoning.

Regarding argument 3, the "bald conclusory statements regarding motivation" were taken straight from the references with citations provided. As stated above, the fact that applicant disagrees with the motivation does not show that the motivation was hindsight or without support. Furthermore, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). There must be a motivation, but it can be found in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In addition to the motivation provided by Guzman, as stated previously, it is obvious to combine prior art elements according to known methods to yield predictable results, as would be the case here.

Regarding argument 4, this is exactly what is taught by Galan and Guzman. In Guzman, *asd* expression is required for cell survival, if the gene is not expressed (for whatever reason) the cells die. Galan discloses a promoter system that allows one to control whether the essential gene linked to the promoter is expressed based on the presence of arabinose. Therefore, in the absence of arabinose (i.e., non-permissive environment), the cell dies and in the presence of arabinose (i.e., the permissive environment) the cell survives. Moreover, it is noted that the idea of biological containment using system whereby a particular environment or nutrient is required for survival is hardly new; even popular movies have used this idea.

The rejection of claims 61-62, 64, 70-73, 83-86, 89-90, and 94 under 35 U.S.C. 103(a) as being unpatentable over Galan *et al.* (Gene, 94:29-35, 1990) in view of Glick *et al.* (Molecular Biotechnology, Principles and Applications of Recombinant DNA, 1994, ASM Press, pp. 90-92), is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That there is no teaching or suggestion in either Galan or Glick to create an environmentally limited viability system wherein a cell is viable in one environment and not

viable in another. Applicant reiterates the teachings of Galan and Glick, stating that Galan merely teaches the use of "balanced-lethal" technology, where the *asd* gene is deleted from the bacterial chromosome and is supplied on a plasmid, to serve as a selection pressure to maintain the plasmid. Applicant also states that there is no teaching or suggestion in Galan to regulate the expression of *asd* and state that *asd* is constitutively expressed in all environments.

2. That the examiner is using hindsight reasoning and making bald general statements regarding the motivation to combine the references.

3. That the examiner is incorrect in suggesting that high levels of *asd* expression is a problem in the art, and that, if high level *asd* expression were a problem, a person skilled in the art would not link *asd* to the temperature sensitive promoter of Glick.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, Galan discloses a system where *asd* expression is required for cell survival. Glick discloses a promoter that is temperature dependent and discloses reasons one would want to use such a promoter. If one where to take the system of Galan and use the promoter of Glick (for the reasons Glick discloses), one would have an "environmentally limited viability system wherein a cell is viable in one environment and not viable in another." The fact that Glick provides different reasons that applicant has used does not render the combination non-obvious. Finally, applicant has stressed the fact that, in Galan, the *asd* gene is constitutively expressed, as if this somehow makes these cells unsuitable for the instant invention. It is noted that the "balanced-lethal" plasmid maintenance system is a preferred embodiment of the instant invention (see page 16, lines 25-30 of the instant specification).

Regarding argument 2, hindsight reasoning requires one to use teachings found only in the instant application rather than teachings found in the art prior to the instant invention. In the instant case, the examiner has referenced motivations that were expressly stated in the art (supported by citations); thus, no improper hindsight reasoning was used. Applicant may disagree with the motivation presented, but this does not mean that hindsight reasoning was used.

Regarding argument 3, the examiner has referred to teachings in the art. As stated by Glick, "a high level of continual expression of a cloned gene is often detrimental to the host cell, because it creates an energy drain, thereby impairing host cell functions" (page 90, paragraph 2). While Glick does not specifically refer to *asd*, the above statement is well known in the art and

widely accepted. This is the reason that plasmids generally require some sort of positive selection, a fact accepted even by applicant (as evidenced by the instant specification, page 16, lines 20-30). To support their argument that high level *asd* expression, applicant has asserted that Galan notes that their cells were stable and had normal growth. However, applicant has not pointed out where this statement can be found and the examiner is unable to find any such statement. To the contrary, while Galan shows that the plasmid was stably maintained, there is no comparison of cell growth between normal cells and the altered cells. Therefore, since the art (not only Glick, but Galan and the cited US Patents) teaches that high level expression of a cloned gene is often detrimental, the examiner has no reason to dismiss the idea (disclosed by Glick) that one would wish to control transcription using a temperature sensitive promoter. Moreover, it is obvious to combine prior art elements according to known methods to yield predictable results, as would be the case here.

The rejection of claims 61-63, 67, 70-73, and 83-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss (US Patent 5,840,483) in view of Guzman *et al.* (J. Bacteriol., 177:4121-4130, 1995), is maintained for the reasons set forth in the previous office action.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicant argues:

1. That Curtiss describes a plasmid maintenance system that ensures that the plasmid vector will be maintained. Applicant asserts that the "balanced-lethal" technology of Curtiss cannot accomplish effective biological containment because the vaccine cells survive in and out of the host due to the presence of the essential gene on the plasmid which is constitutively expressed.

2. That there is no teaching or suggestion to create an environmentally limited viability system where a cell is viable in one environment and not viable in another.

3. That all claim limitations must be taught or suggested by the prior art and that "in the present case, critical limitations and recitation of the present claims are only taught by Applicant's specification (and not by any of the cited prior art)."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the "balanced-lethal" plasmid maintenance system is a preferred embodiment of the instant invention (see page 16, lines 25-30 of the instant specification). As to the assertion that "balanced-lethal" technology cannot accomplish biological containment, Curtiss states "the inclusion of asd, and thus dap, mutations in strains of bacteria affords biological containment, since such mutant strains are unable to survive in environments other than a carefully controlled laboratory environment" (column 4, lines 1-5). Based on this statement, Curtiss clearly discloses the idea of biological containment based on control of the cell's environment. Guzman teaches a system that allows simple control of *asd* expression, and thus, a system where a cell is viable in one environment and not viable in another.

Regarding argument 2, this is exactly what is taught by Curtiss and Guzman. In Curtiss, *asd* expression is required for cell survival, if the gene is not expressed (for whatever reason) the cells die. Galan discloses a promoter system that allows one to control whether the essential gene linked to the promoter is expressed based on the presence of arabinose. Therefore, in the absence of arabinose (i.e., non-permissive environment), the cell dies and in the presence of arabinose (i.e., the permissive environment) the cell survives. Further, it is obvious to combine prior art elements according to known methods to yield predictable results, as would be the case here.

Regarding argument 3, each claim limitation has previously been addressed with showing where these can be found in the prior art and applicant has not shown any limitation that is lacking.

The rejection of claims 61-63, 67, 70-73, and 83-84 under 35 U.S.C. 103(a) as being unpatentable over Curtiss (US Patent 5,672,345) in view of Guzman *et al.* (J. Bacteriol., 177:4121-4130, 1995), is maintained for the reasons set forth in the previous office action.

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obvious to combine prior art elements according to known methods to yield predictable results, as would be the case here.

Regarding argument 3, each claim limitation has previously been addressed with showing where these can be found in the prior art and applicant has not shown any limitation that is lacking.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645